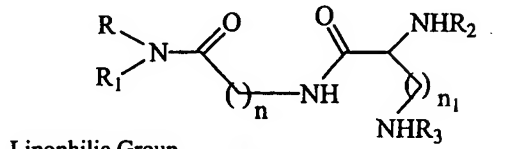
Figure 1A

I. Diamino Carboxylic acid-Based Cationic Lipid



Lipophilic Group Linker Head Group

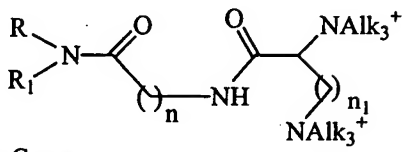
n = 1-3, n_1 = 2-5

R,R_1 = C12-C22 saturated or unsaturated (1-4 double bonds) alkyl chain.

R_2,R_3 = H, acyl, alkyl, carboxamidine, *N*-alkyl (aryl, acyl, PEG) substituted carboxamidine, PEG, or combination thereof.

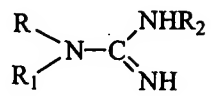
Alk = methyl, hydroxyethyl or combination thereof.

II. Quarternary Diamino Carboxylicacid-Based Cationic Lipid



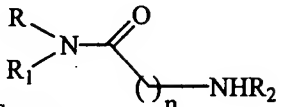
Lipophilic Group Linker Head Group

III. Guanidinium-Based Cationic Lipid



R_2 = H, acyl, alkyl, PEG

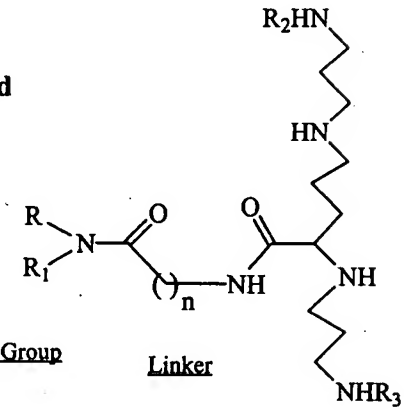
IV. Mono Amino-Based Cationic Lipid



Lipophilic Group Linker Head Group

R_2 = H, carboxamidine, *N*-alkyl (aryl, acyl, PEG) substituted carboxamidine, PEG

V. Polyamine-Based Cationic Lipid



Lipophilic Group Linker Head Group

R_2=R_3=H
R_2=PEG, R_3=H
R_2=H, R_3=PEG

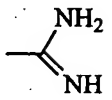
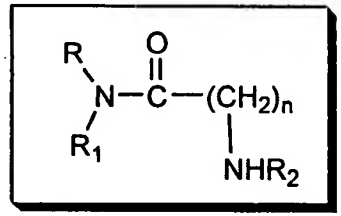
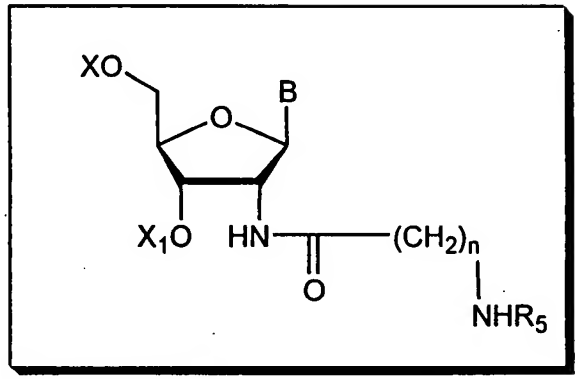
R_1=R_3 = H, or 

Figure 1B: Mono Amino-Based Cationic Lipid

Class IV



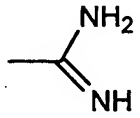
Class V



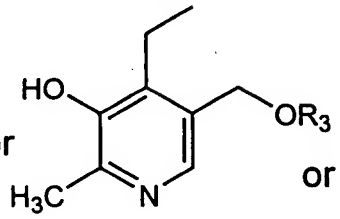
R, R_1 = C12-C22 saturated or unsaturated (1-4 double bonds) alkyl chain.

n = 2-6

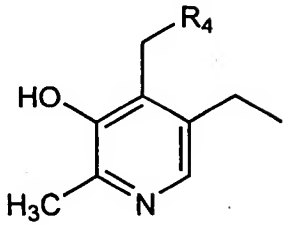
R_2= H,



or



or



R_3= H, PO_3H_2, PEG
R_4 = OH, NH_2, =O, O-PEG
R_5 = H, carboxamidine
X= X1=R, R1
X=R, X1=R1, X=R1, X1=R
X=PEG, X_1=H
X=H, X_1=PEG
B= nucleic acid base (modified or unmodified) or H

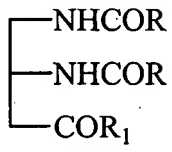
PEG: or PEG 2000 carbonyl, PEG 5000 carbonyl

methoxypolyoxyethylene carbonyl
(Ave. Mol. Wt. = 2000 or 5000)

CO-PEG2000 - amide
COOPEG - carbamate

Figure 1C

General formula:



R = saturated or unsaturated (1-4 double bonds) alkyl chains (12-22C)

R_1 = TREN, N,N'-di-carboxamidine TREN, lysyl, arginyl, ornithyl, homoarginyl, histidyl, aminopropylimidazole, spermine carboxylic acid.

Figure 2

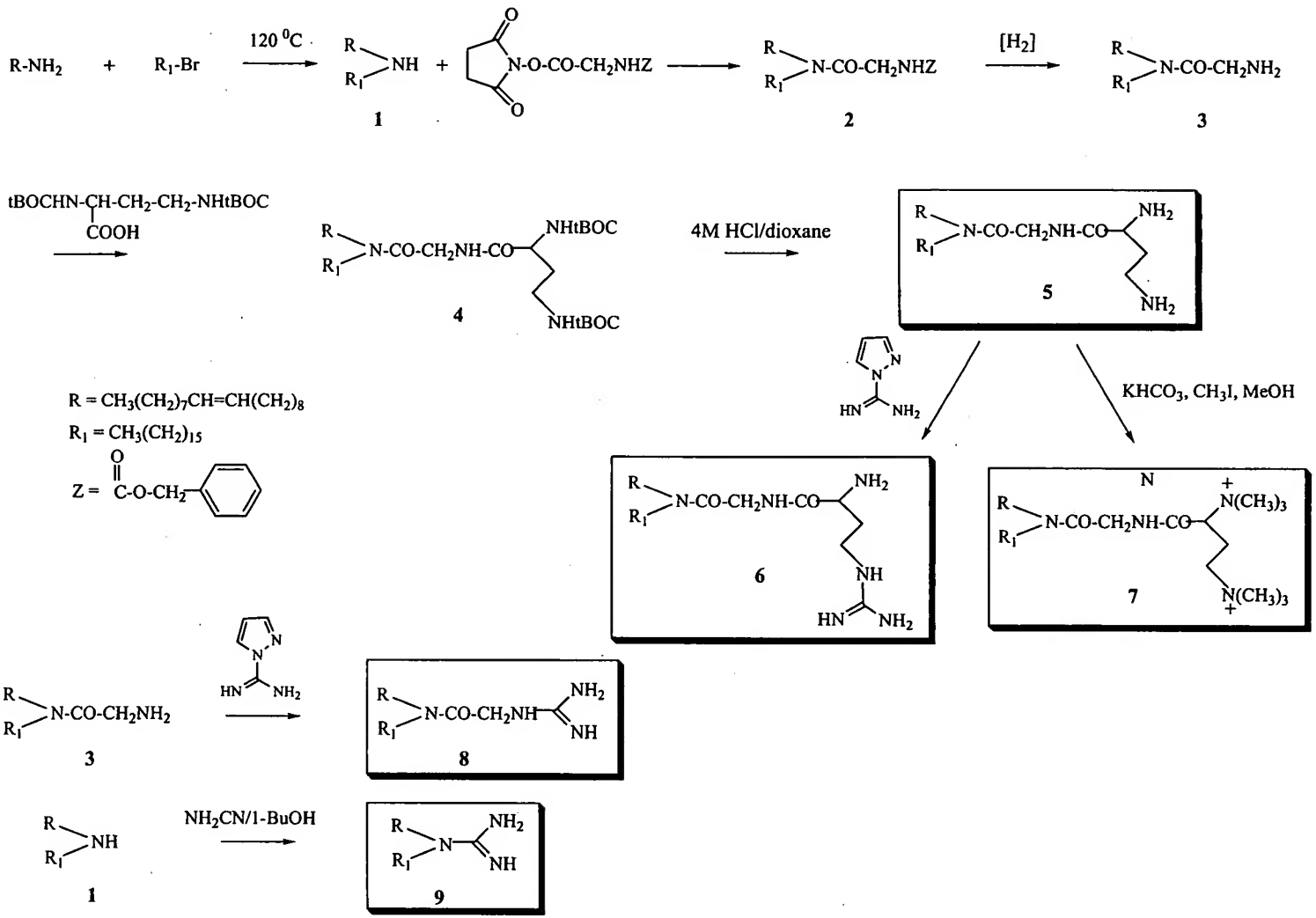

R-NH2 + R1-Br
120 °C
1
2
3
[H2]
tBOCHN-CH-CH2-CH2-NHtBOC
COOH
4
4M HCl/dioxane
5
R = CH3(CH2)7CH=CH(CH2)8
R1 = CH3(CH2)15
Z =
KHCO3, CH3I, MeOH
6
7
8
9
NH2CN/1-BuOH

Figure 3: Synthesis of DS 46596 (12)

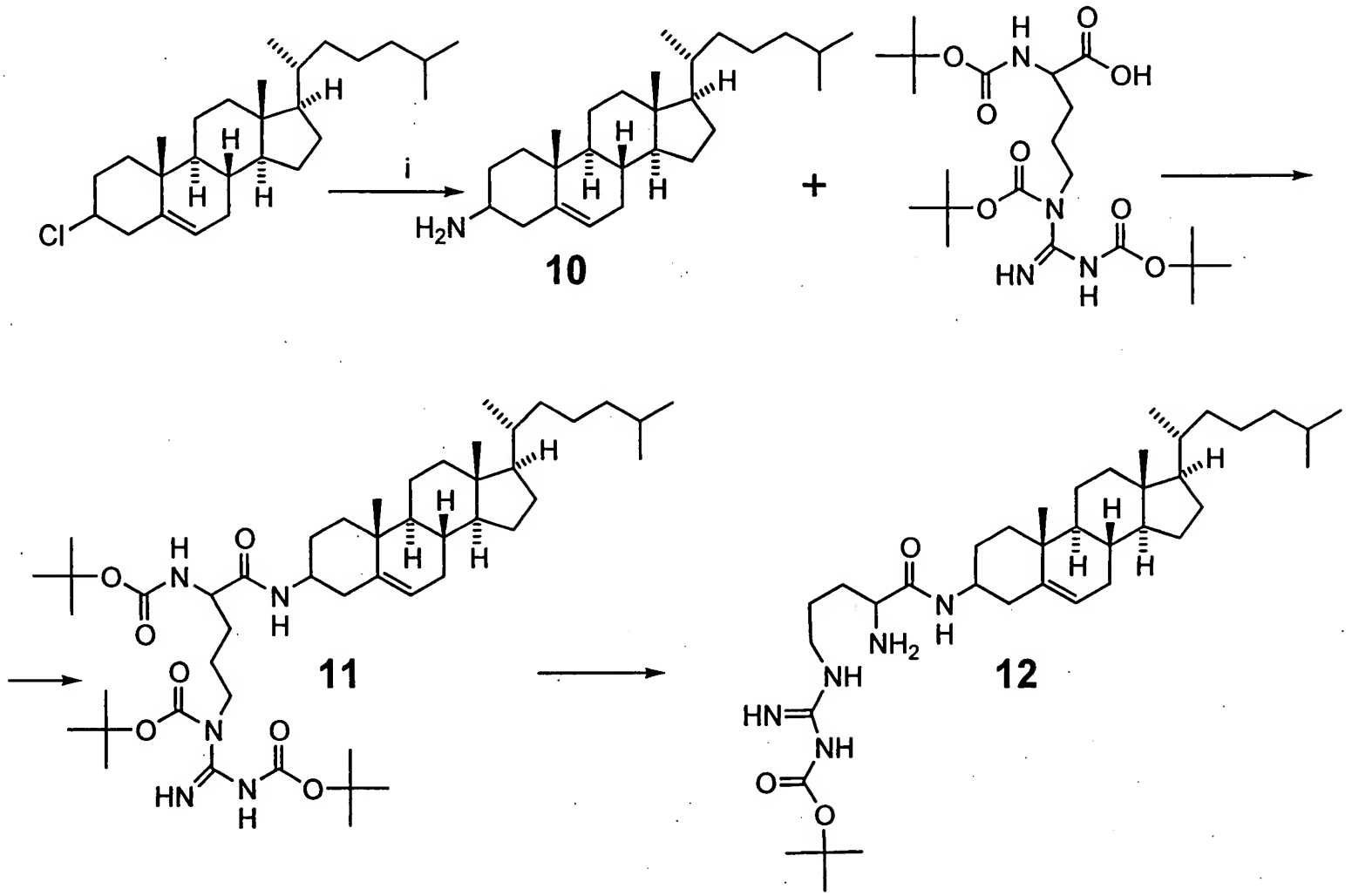


Figure 4: Synthesis of PH 55933 (15), 55938 (16)

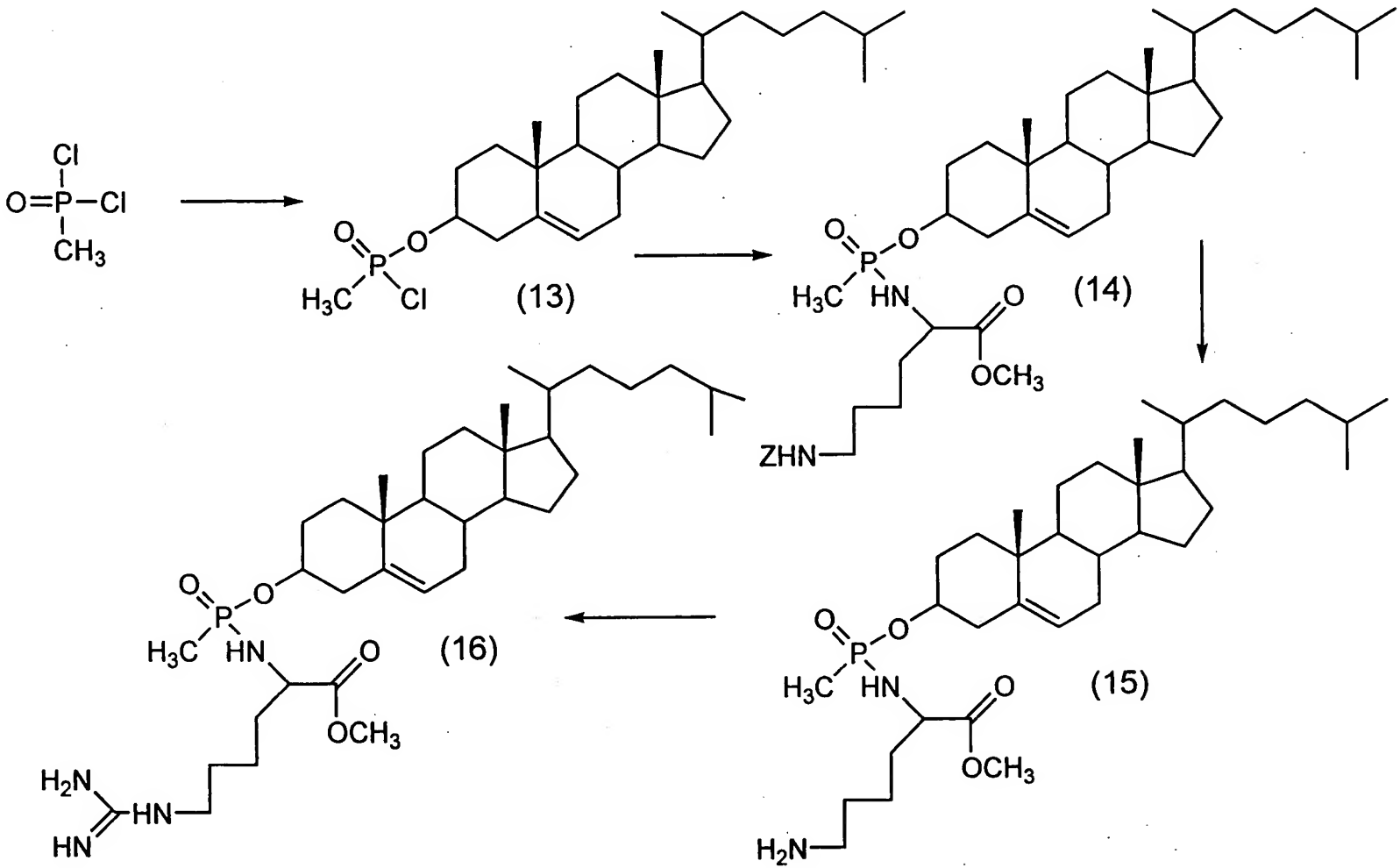


Figure 5: Synthesis of PH 55939 (17)

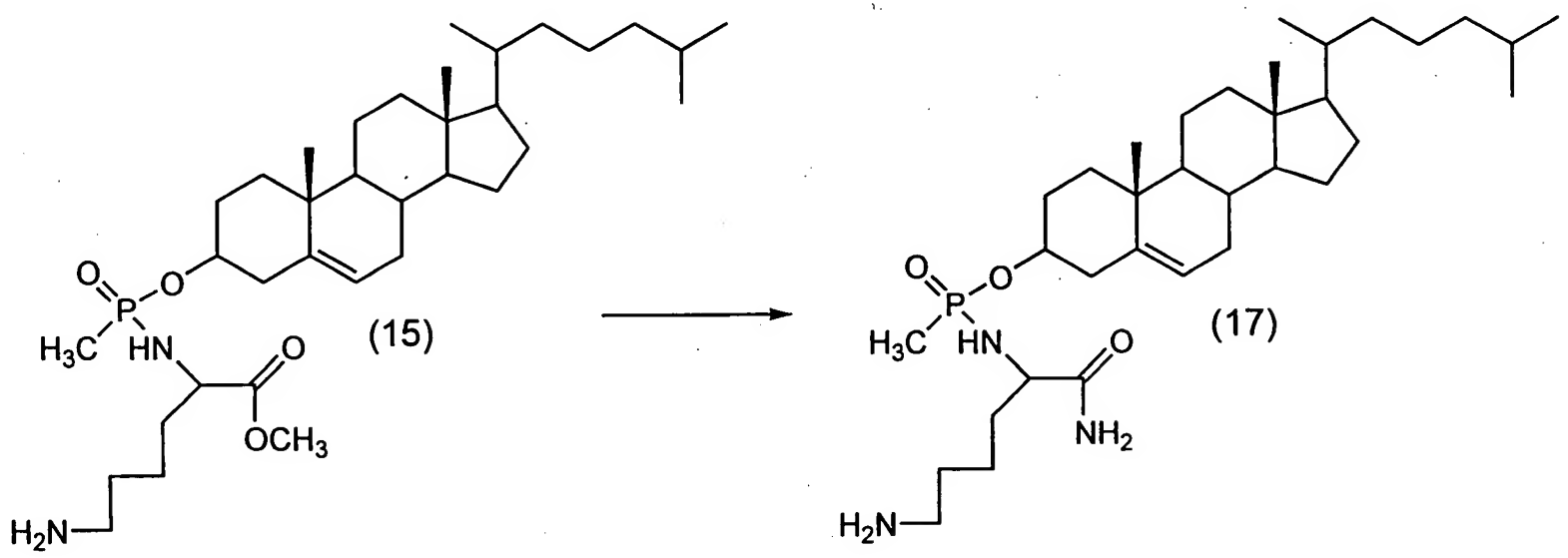


Figure 6: Synthesis of PH 55941 (18), 55942 (19)

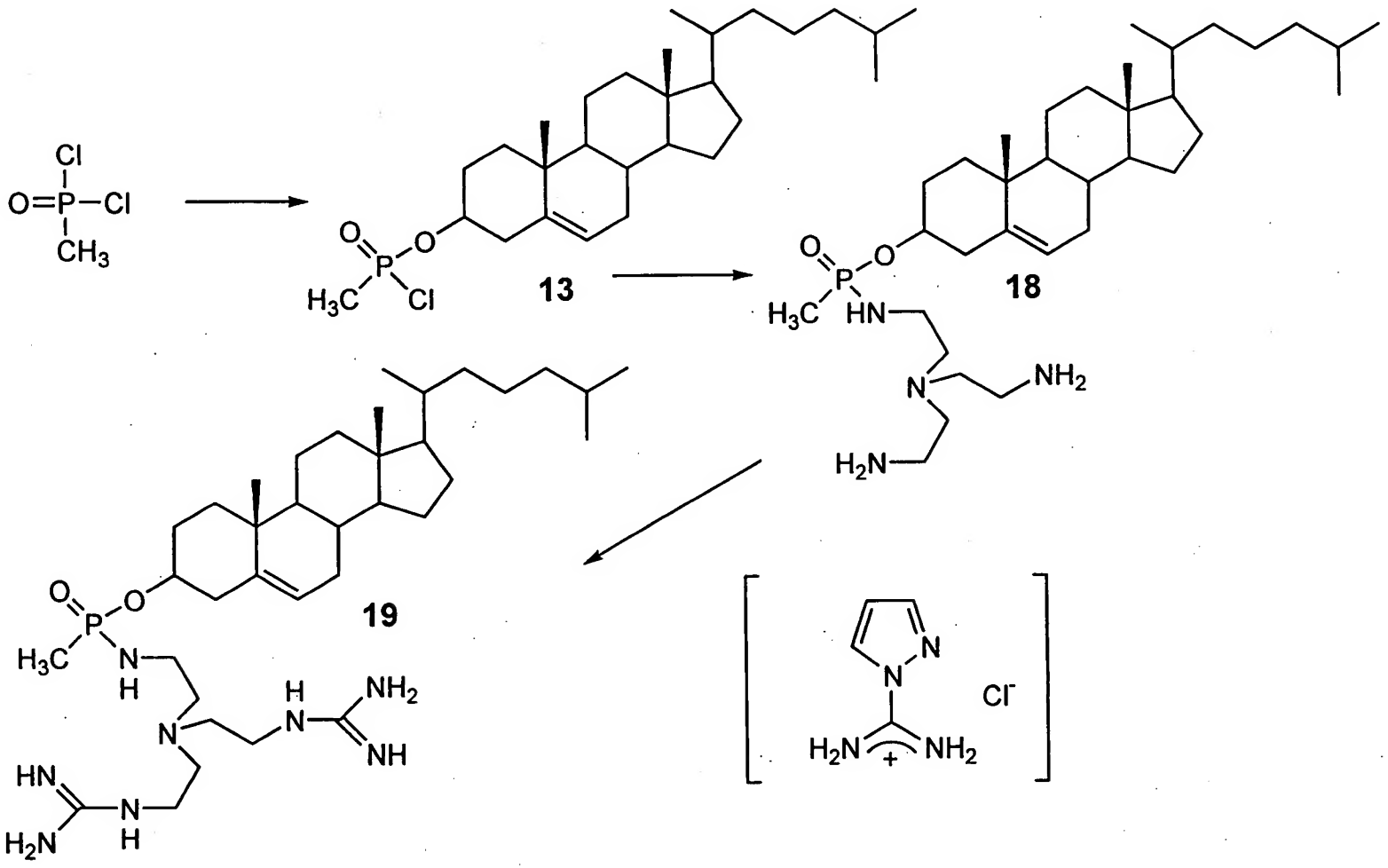


Figure 7: Synthesis of PH55943 (20)

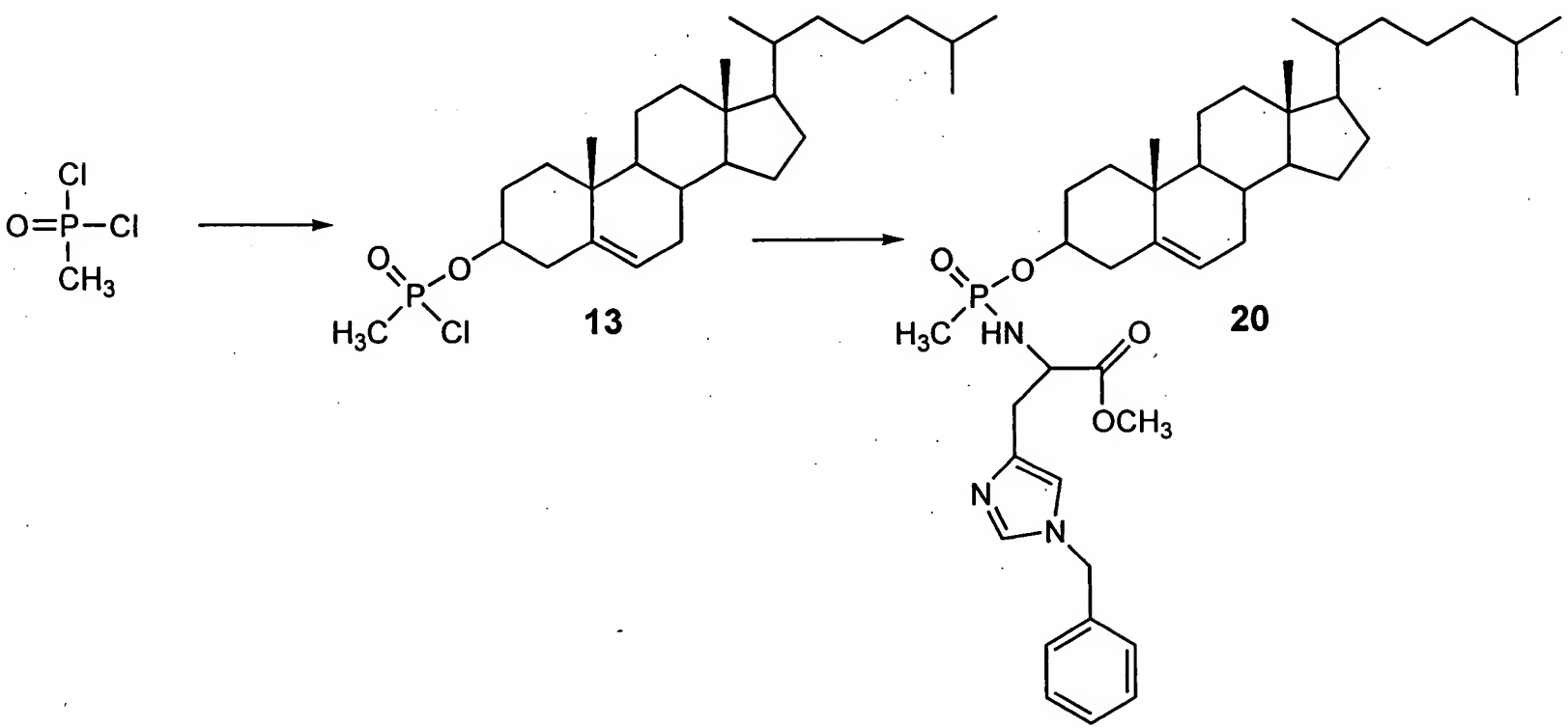


Figure 8: Synthesis of PH 55945 (21)

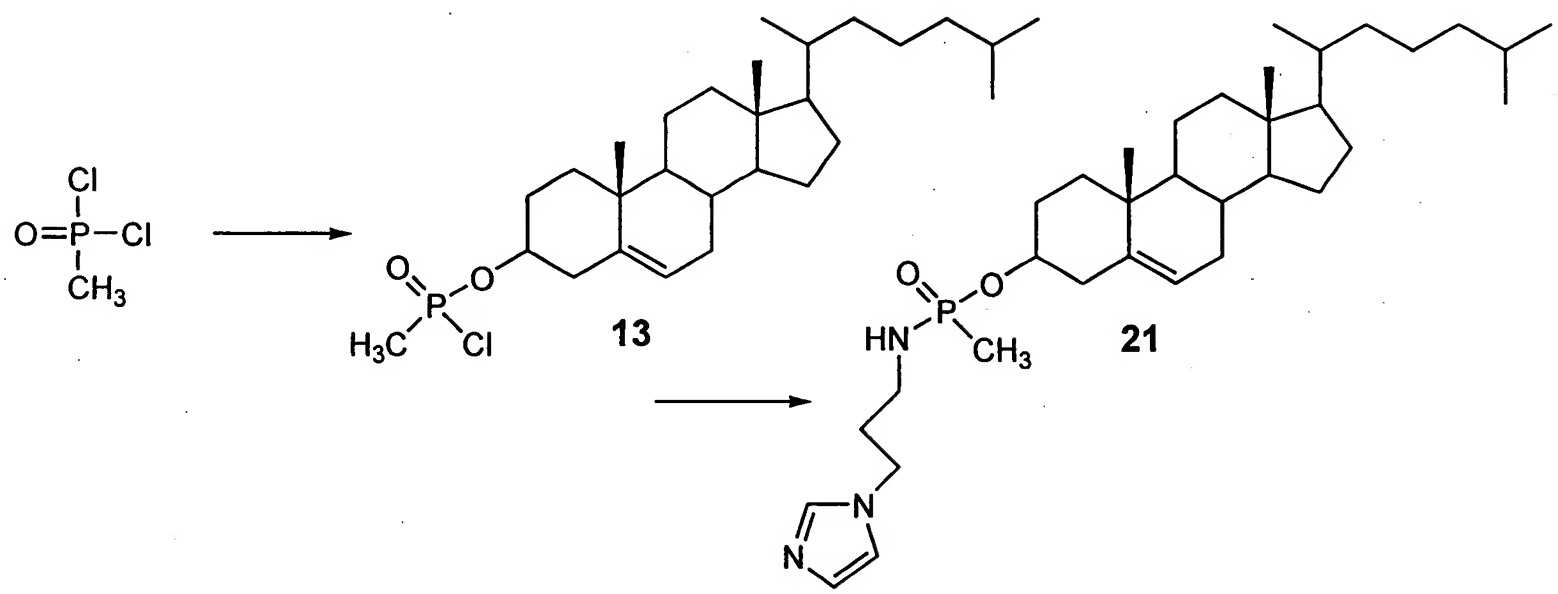
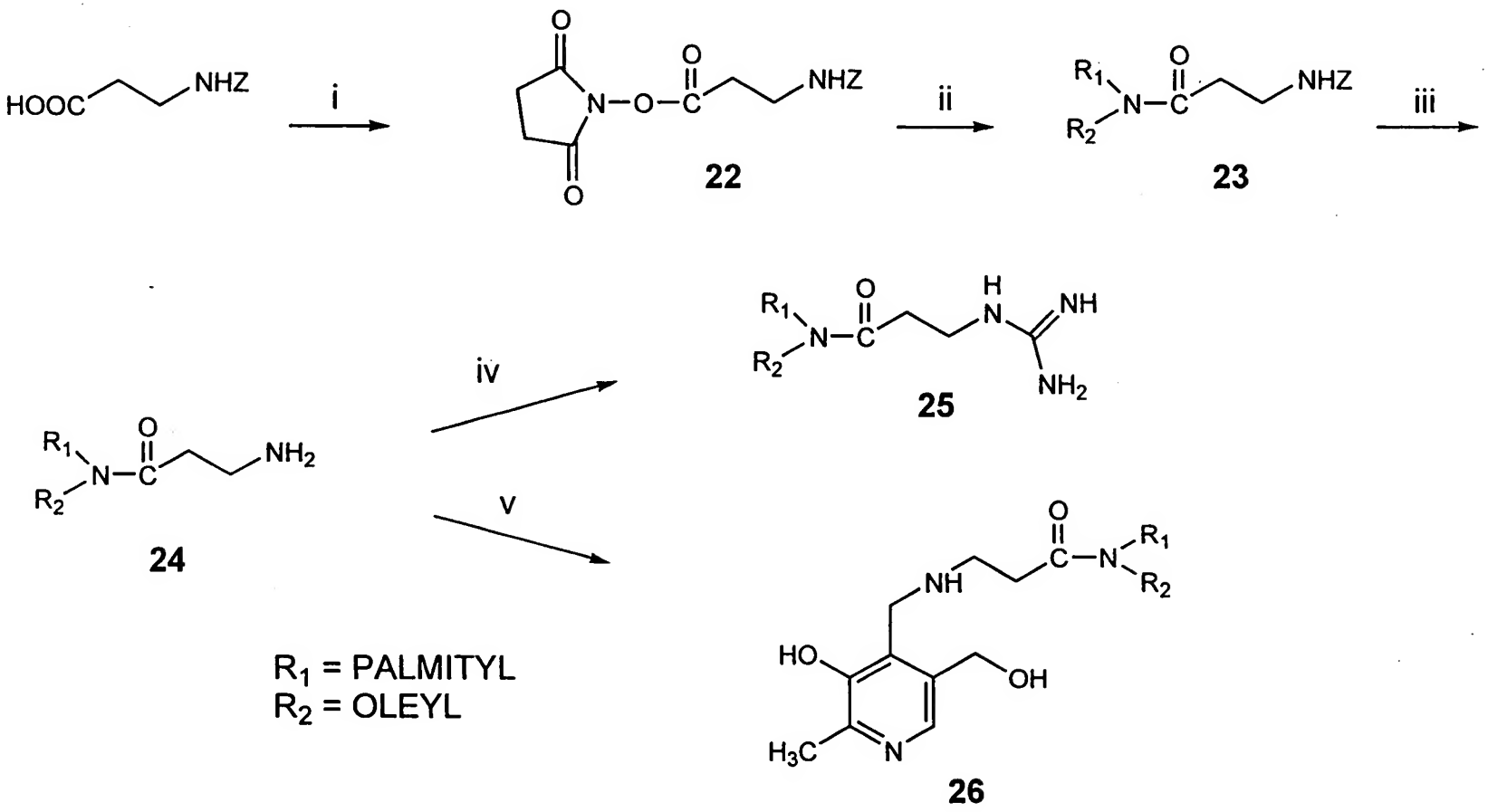
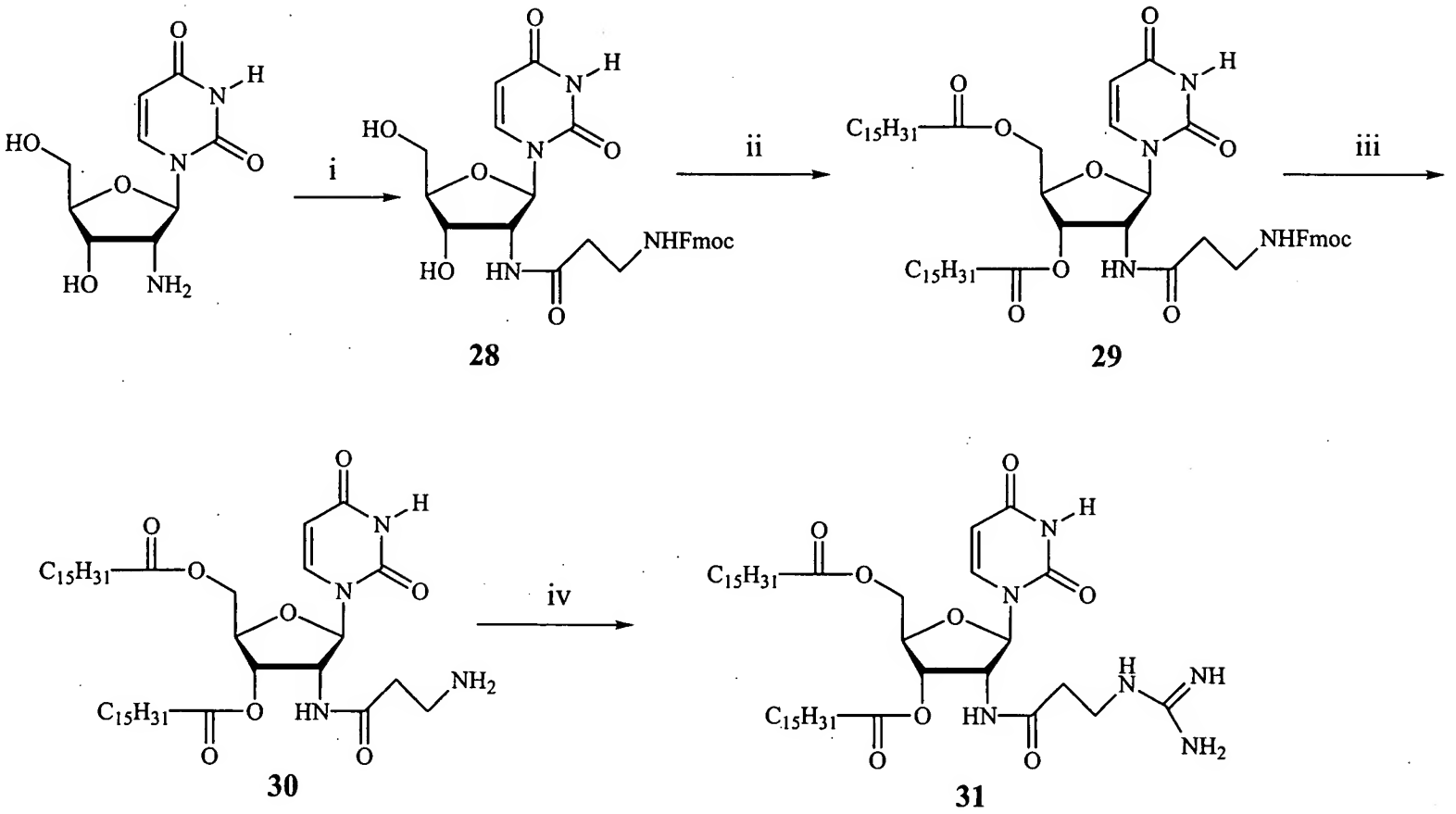


Figure 9:VITAMIN B_6 and β-Ala-BASED CATIONIC LIPIDS



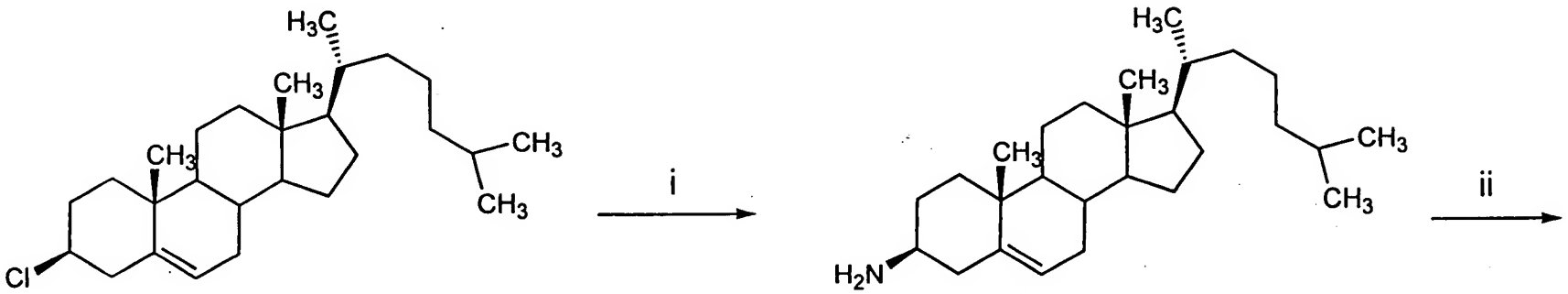
REAGENTS AND CONDITIONS: i) N-hydroxysuccinimide, DCC; ii) HNR_2, Et_3N; iii) 10% Pd/C, 1,4-cyclohexadiene; iv) a: pyridoxal/EtOH, b: $NaBH_4$; v) 1*H*-pyrazole-1-carboxamidine/THF-MeOH

Figure 10

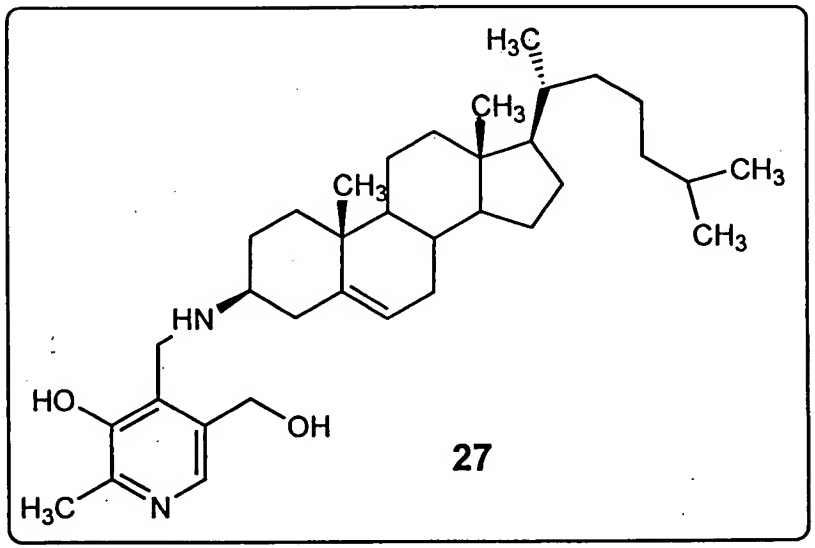


Reagents and conditions: i) N-Fmoc-b-Ala, EEDQ/MeOH; ii) $C_{15}H_{31}COCl$/Py; iii) morpholine/CH_2Cl_2; iv) 1*H*-pyrazole-1-carboxamidine/THF-MeOH

Figure 11: VITAMIN B_6 -CHOLESTEROL CONJUGATE



Cholesteryl chloride



27

REAGENTS AND CONDITIONS: i) NH_3/MEOH; ii) reductive amination of pyridoxal

FIGURE 12A

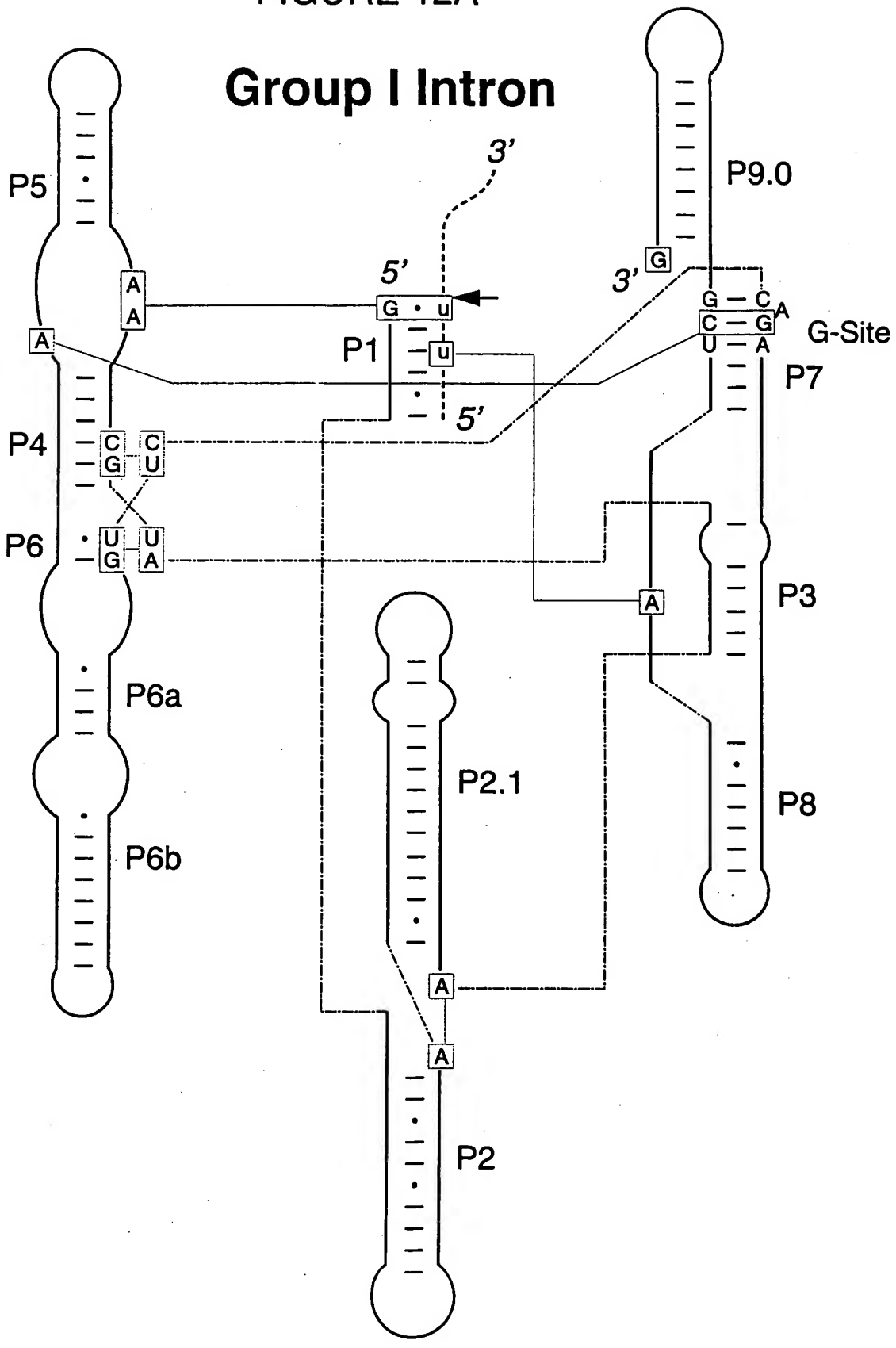


FIGURE 12B

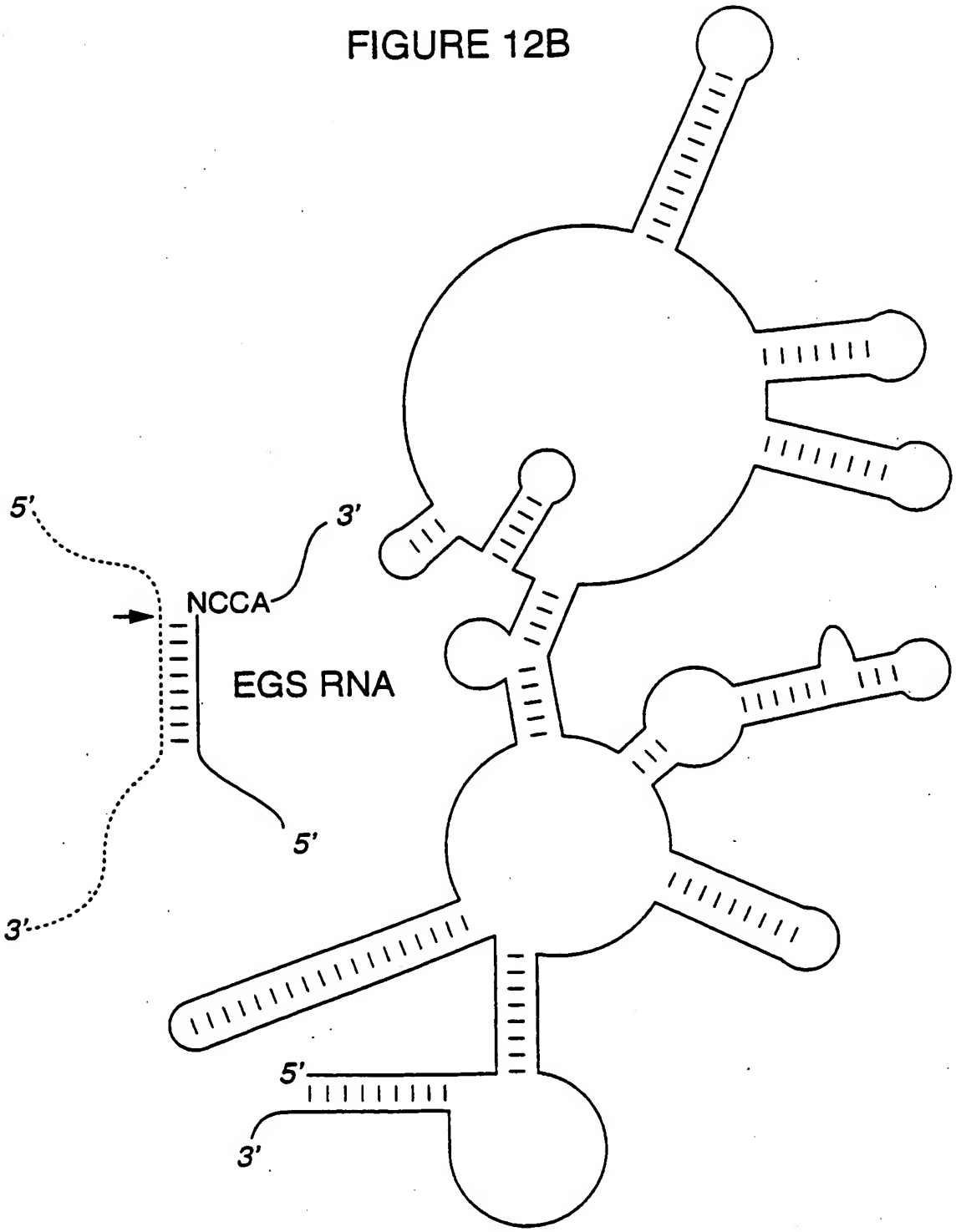


FIGURE 12C

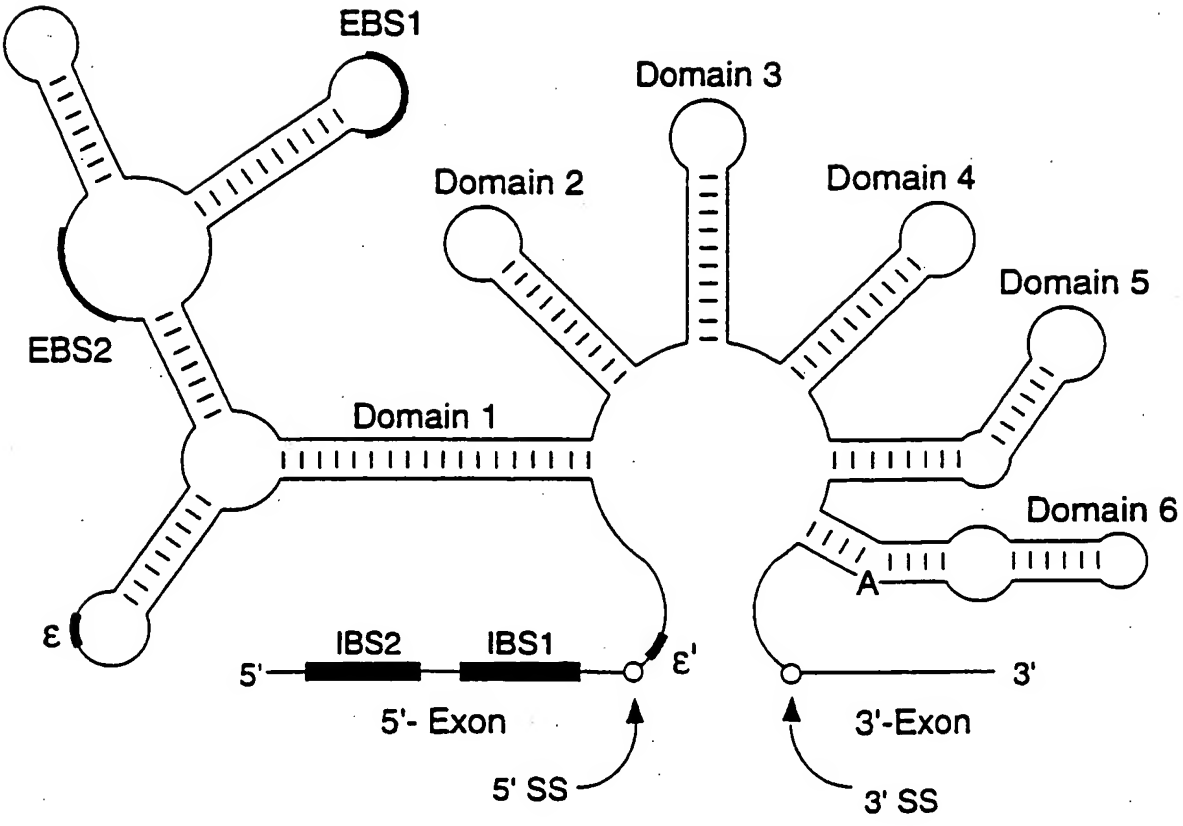

EBS1
Domain 3
Domain 2
Domain 4
Domain 5
EBS2
Domain 1
Domain 6
A
ε
IBS2
IBS1
ε'
5'
3'
5'- Exon
3'-Exon
5' SS
3' SS

Figure 12D

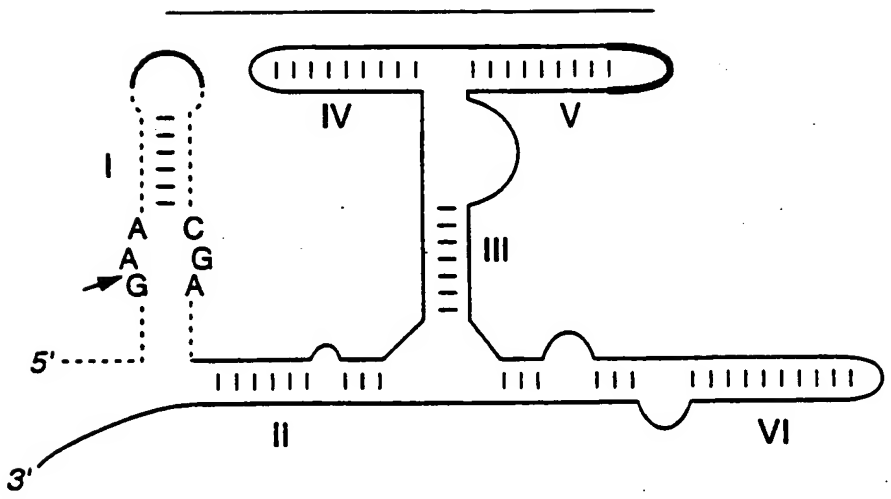


FIGURE 12E

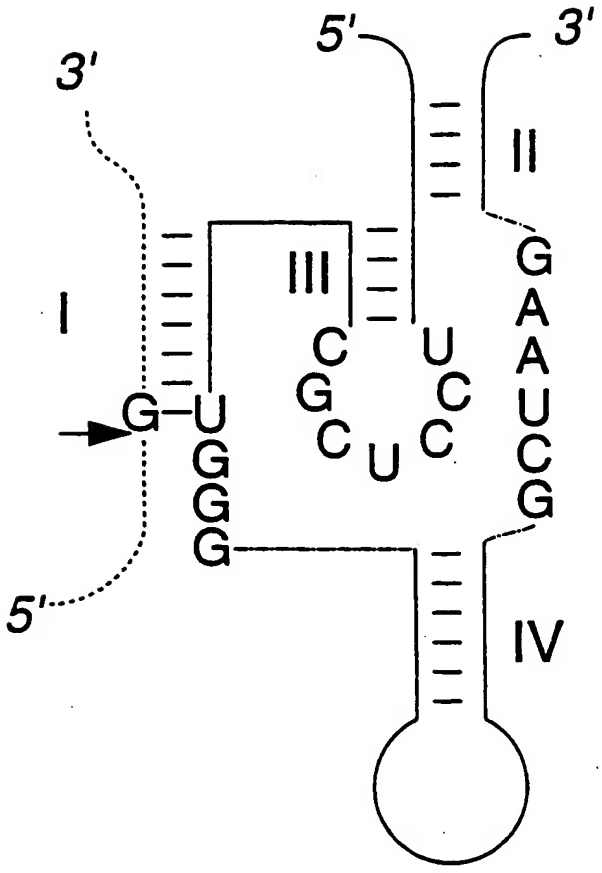


FIGURE 12F

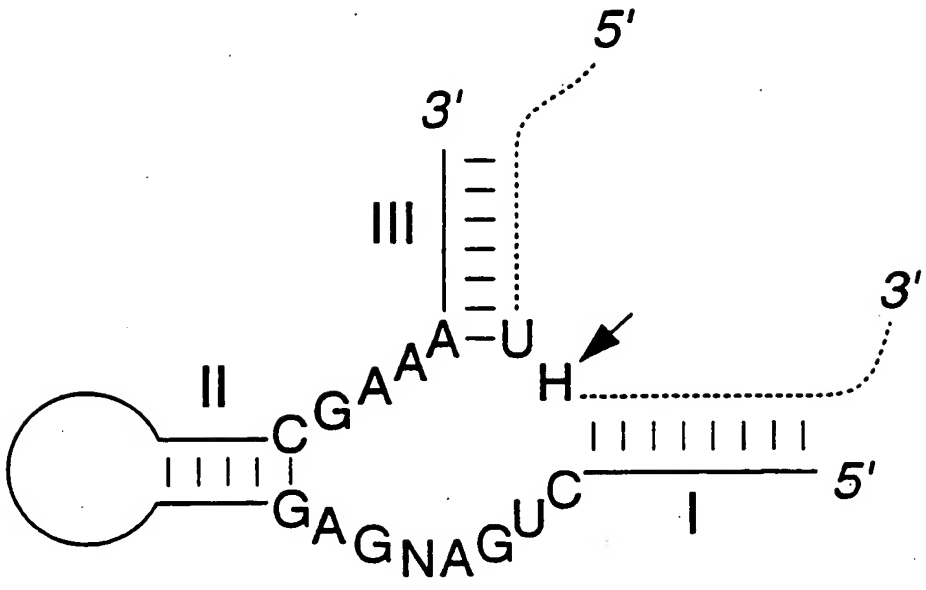
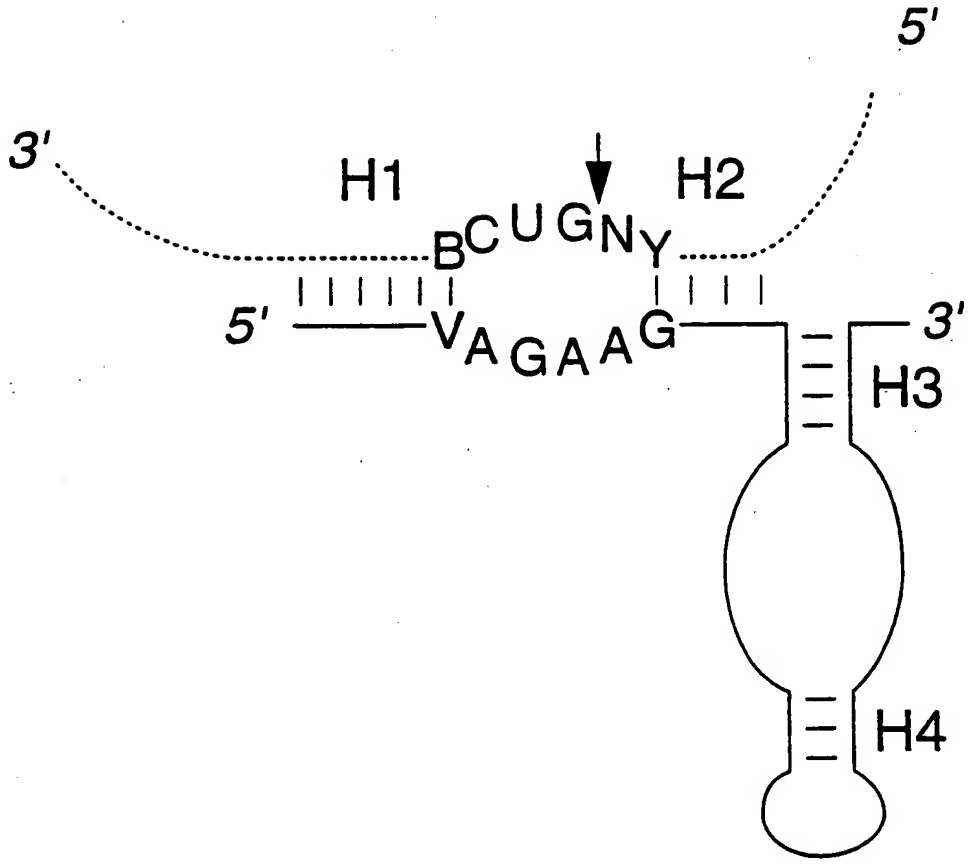
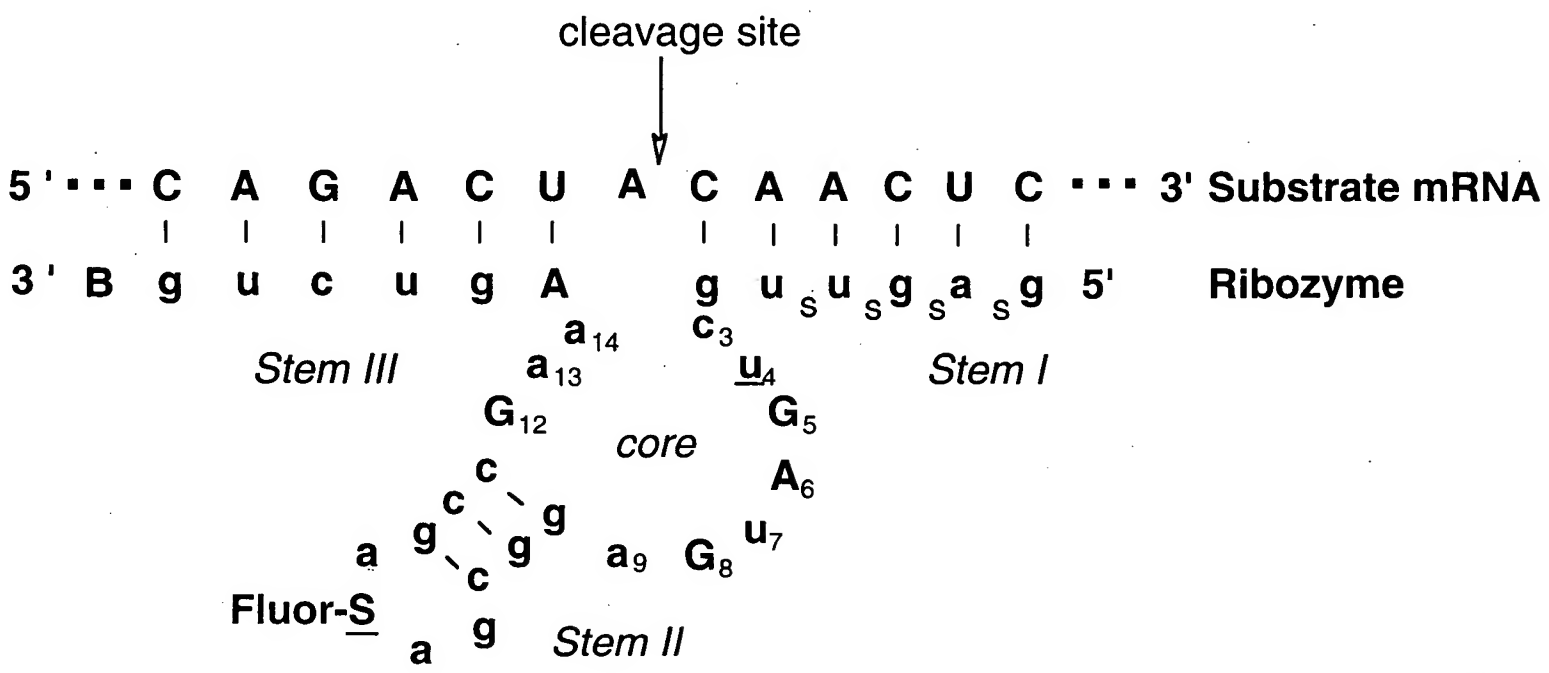


FIGURE 12G





Lowercase: 2'-*O*-Me
Uppercase: ribonucleotide
B: inverted deoxy abasic
s: phosphorothioate
S: c6 dT amino linker

Figure 13

Figure 14

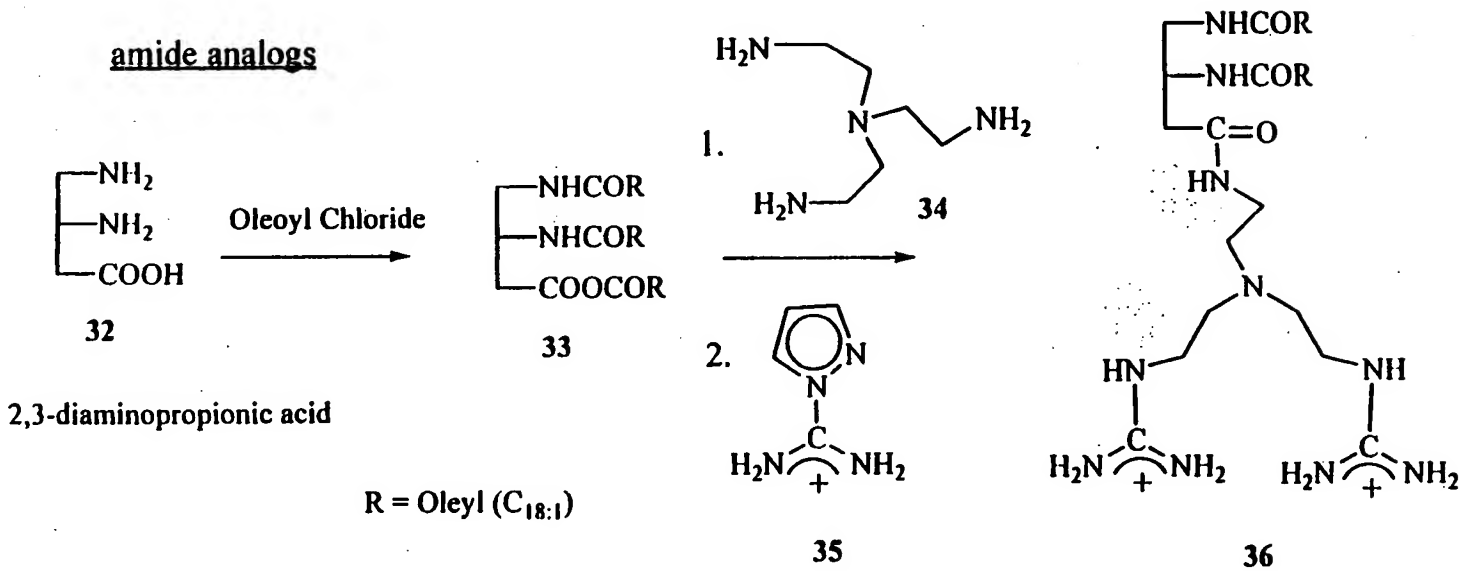

amide analogs
NH2
NH2
COOH
32
Oleoyl Chloride
NHCOR
NHCOR
COOCOR
33
2,3-diaminopropionic acid
R = Oleyl (C18:1)
1.
H2N
N
NH2
H2N
34
2.
N
N
C
H2N
NH2
35
NHCOR
NHCOR
C=O
HN
N
HN
NH
C
H2N
NH2
C
H2N
NH2
36

Figure 15: Concentration of Intact Ribozyme after Intravenous Administration of EPC:CHOL:DOTAP:DSPE-PEG$_{2000}$ Liposome Encapsulated Ribozyme

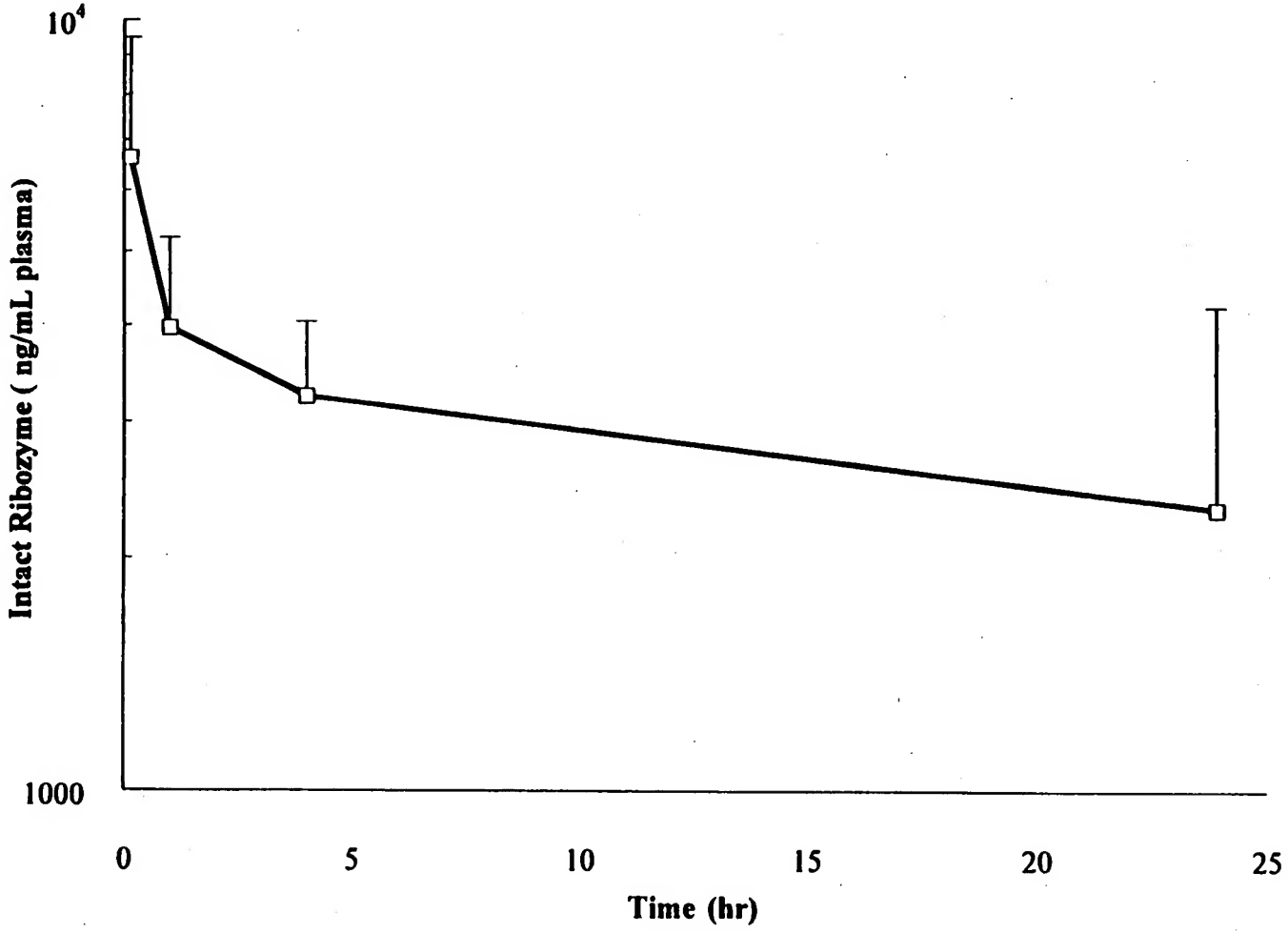


Figure 16: Inhibition of IMPDH-2 mRNA Expression in Jurkat Cells Treated for 24 h with IMPDH antisense molecule + 5 µg/ml Formulation ID No. 345

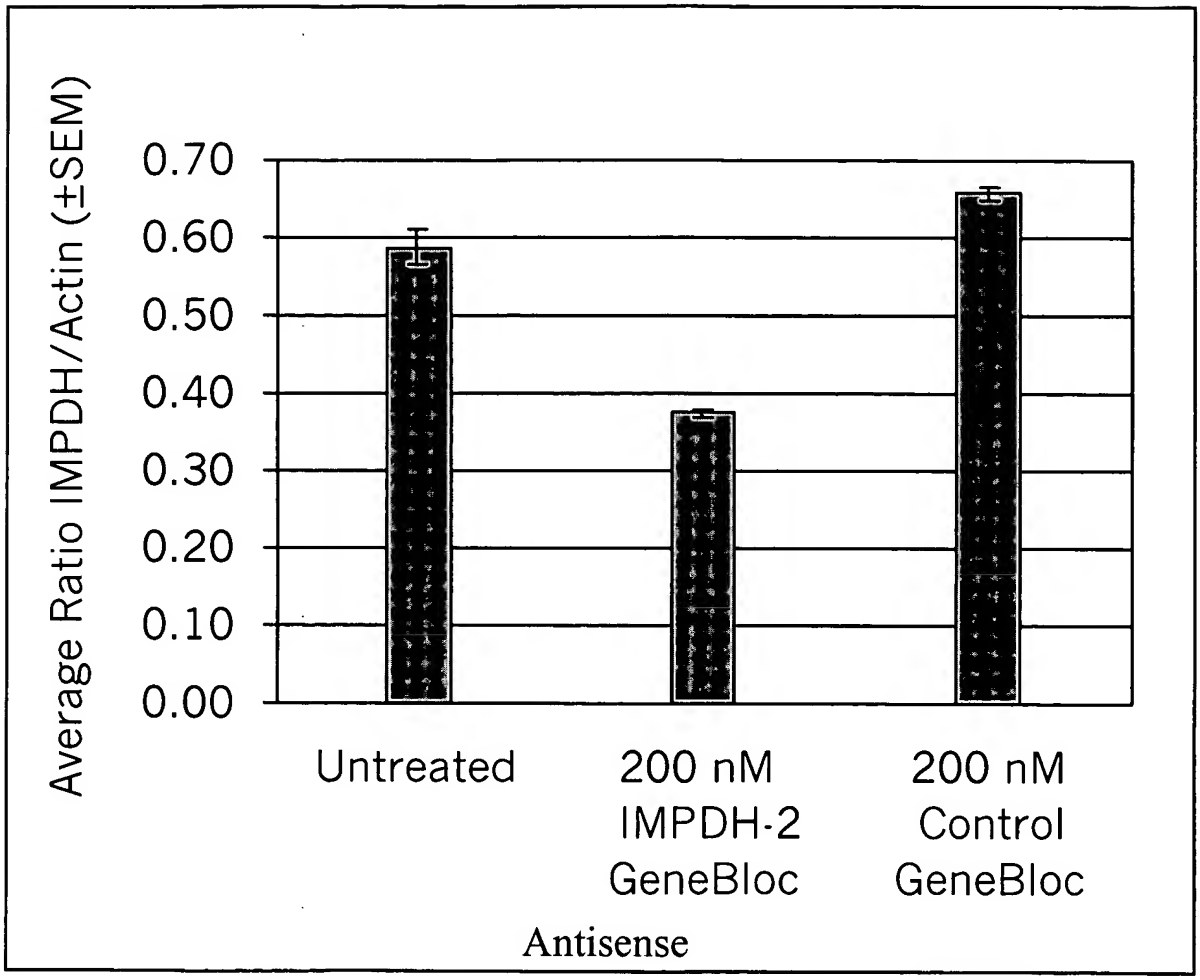


Figure 17: Inhibition of IMPDH-2 mRNA Expression in Jurkat Cells Treated for 24 h with IMPDH Antisense molecules+ Formuation ID NO: 323

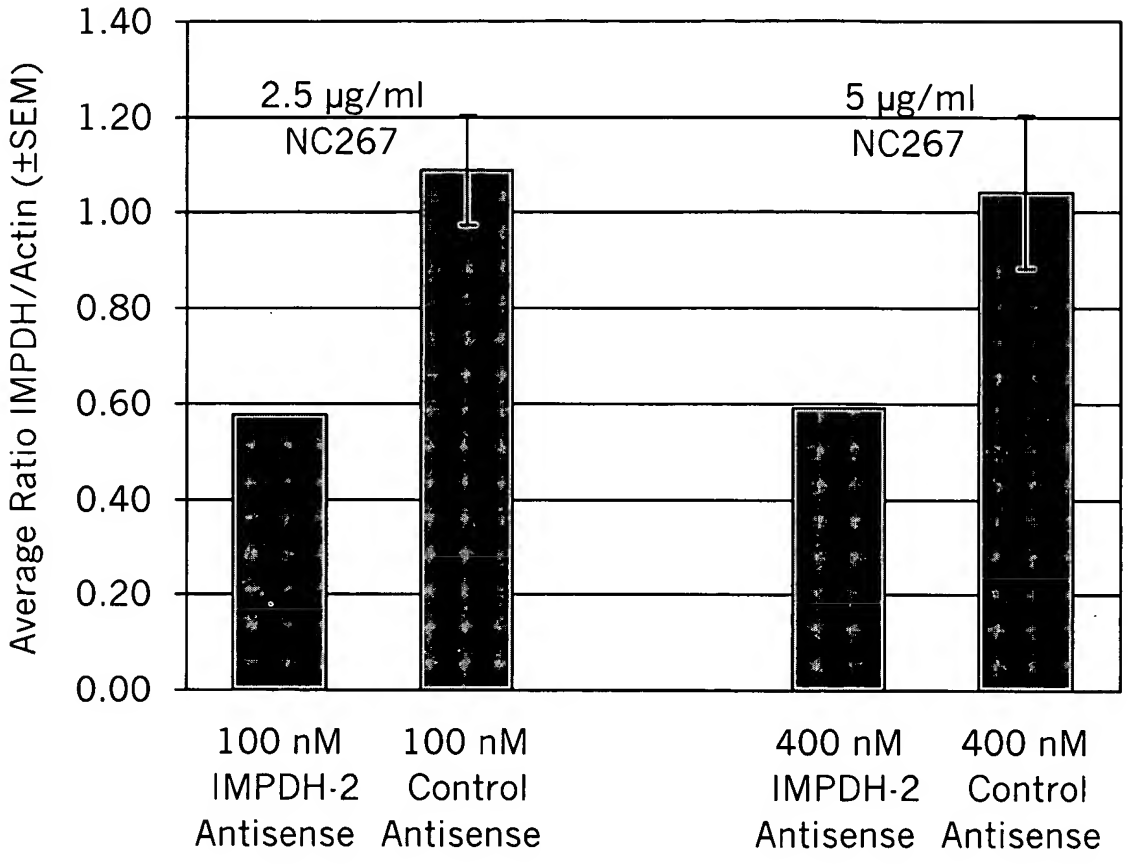


Figure 18: Inhibition of IMPDH-2 mRNA Expression in Jurkat Cells Treated for 24 h with IMPDH antisense molecules + Formulation ID NO: 333